İNVAZİF FUNGAL İNFEKSİYONLAR:

ERKEN ve DOĞRU TEDAVİ?

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İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

MANTARLAR…

- Dünyadaki mantar türü sayısı: **5 milyon**
- Tanımlanmış olan tür sayısı: **120 bin**
- İnsanda hastalık yapan tür sayısı: **300**
- Hastalık etkeni olarak sık görülen tür sayısı: **20-25**

2000'li yılların başında HIV/AIDS hastalarında
yılda 1 milyon dissemine kriptokok enf. görülmekte;
600 bin olgu kaybedilmekte idi

Park, B. J. *et al.* Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS* **23**, 525–530 (2009).

Journal of Fungi

MDPI

Review

Global and Multi-National Prevalence of Fungal Diseases—Estimate Precision

Mantar hastalıkları > 1milyar insanı etkiliyor: >1.5 milyon ölüm (her yıl)

- ✓ 3.000.000 kronik pulmoner aspergilloz
- ✓ 223.000 kriptokok menenjiti (HIV/AIDS)
- ✓ 700.000 invaziv kandidiyazis
- ✓ 500.000 PJP
- ✓ >300.000 İnvazif aspergilloz (10 milyon risk altındaki kişide)
- ✓ 100.000 Histoplazmoz
- ✓ 10.000.000 Astım
- ✓ 1.000.000 Keratit

J. Fungi 2017;3:57-86

Avustralya;

2005-2016,

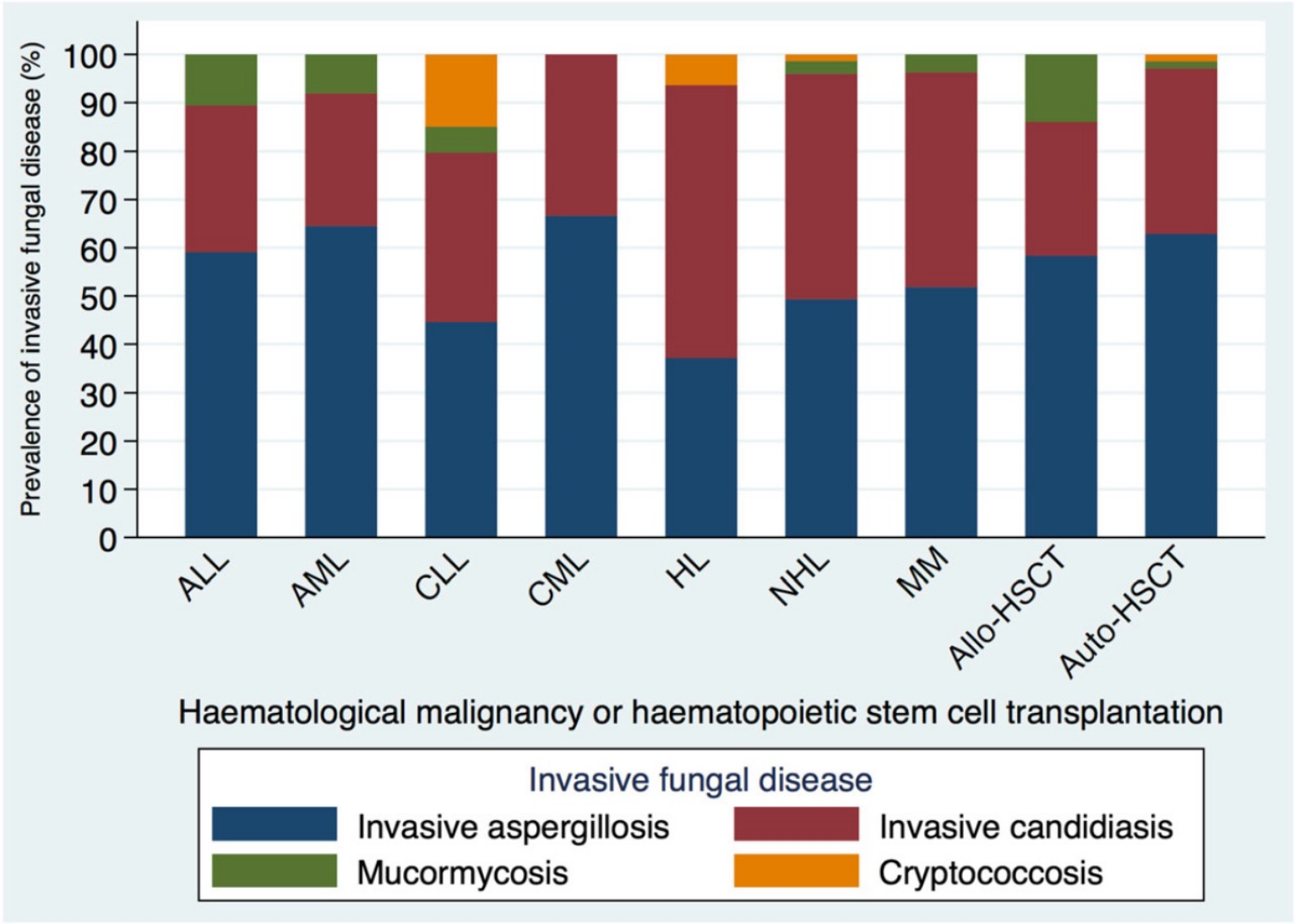
Hematolojik maligniteli : 32,815 hasta, Allo KHN: 335, OtologKHN: 1449 hasta

Table 2 Invasive Fungal Disease Incidence Stratified by Haematological Malignancy and Haematopoietic Stem Cell Transplantation from Index Hospitalisation, 2005 – 2016

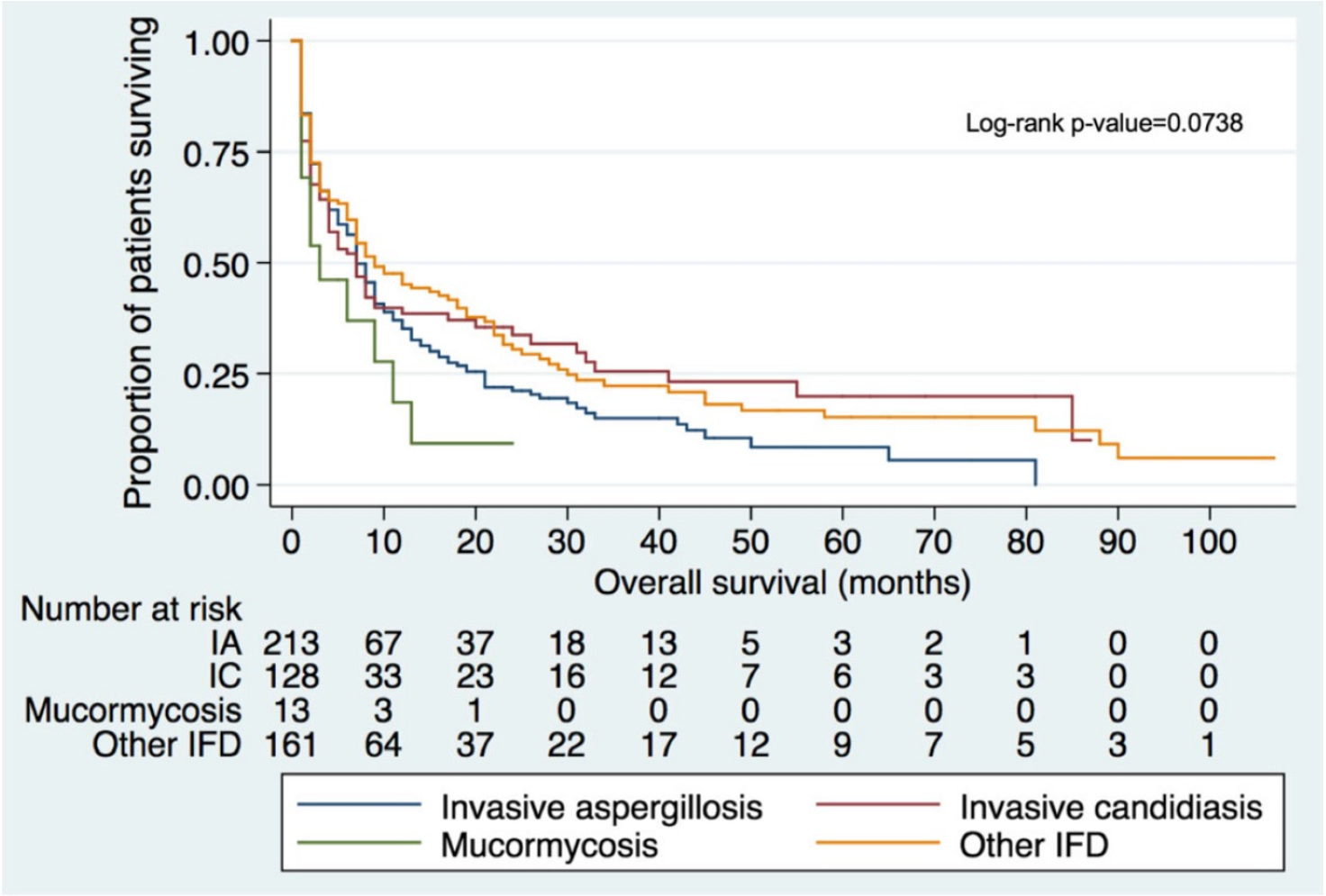
Haematological malignancy and haematopoietic stem cell transplantation	Invasive fungal disease; incidence (%)
Allogeneic-haematopoietic stem cell transplantation (N = 335)	41 (12.2)
Acute lymphoblastic leukaemia (N = 664)	75 (11)
Acute myeloid leukaemia (N = 2,644)	249 (9.42)
Autologous-haematopoietic stem cell transplantation (N = 1,449)	70 (4.83)
Aplastic anaemia (N = 7,121)	101 (1.42)
Chronic lymphocytic leukaemia (N = 3,459)	46 (1.33)
Non-Hodgkin lymphoma (N = 15,267)	192 (1.26)
Multiple myeloma (N = 5,614)	58 (1.03)
Hodgkin lymphoma (N = 2,030)	17 (0.84)
Chronic myeloid leukaemia (N = 1,240)	10 (0.81)
Other haematological malignancies (N = 1,897) [a]	22 (1.16)

[a]Myelodysplastic syndrome patients included in 'Other' due to a small patient cohort.

Valentine et al. BMC Infectious Diseases (2019) 19:274



Valentine et al. BMC Infectious Diseases (2019) 19:274



Akut lösemi, hemodiyaliz, nötropeni, viral enfeksiyon: Mortalitede anlamlı artış

Valentine et al. BMC Infectious Diseases (2019) 19:274

Japonya, 2009, 13787 otopsi, 633 (%4.6) IFI

Table 5 Visceral mycoses in patients with or without leukemia and myelodysplastic syndrome.

Mycosis	Total number 633	Leukemia and MDS 99	Except for leukemia 534
Monopathogen			
Aspergillosis	299	52 (52.5)	247 (47.6)
Candidosis	184	22 (22.2)	162 (31.2)
Cryptococcosis	35	1 (1.0)	34 (6.6)
Mucormycosis	22	5 (5.1)	17 (3.3)
Trichosporonosis	1	0	1 (0.2)
Unknown[†]/others[§]	69	11 (11.1)	58 (11.2)
Complicated[‡]	23	8 (8.1)	15 (2.8)

Medical Mycology 2013;51:522–526

İFİ niçin bu kadar önemli?

EDITORIALS & PERSPECTIVES

The role of antifungal treatment in hematology

Johan A. Maertens,[1] Marcio Nucci,[2] and J. Peter Donnelly[3]

[1]Department of Hematology, Acute Leukemia and Stem Cell Transplantation Unit, University Hospital Gasthuisberg, K. U. Leuven, Leuven, Belgium; [2]Hospital Universitário Clementino Fraga Filho, Universidade Fedeal do Rio de Janeiro, Brazil; [3]Department of Hematology & Nijmegen Institute for Infection, Inflammation and Immunity, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

...tment is started using ... Finally, the crude mortality rate of invasive fungal disease is not that different from the mortality rate of most malignant blood disorders, being around 40%. However, assessing the role of the underlying malignant disease or of invasive fungal disease remains difficult, especially when a postmortem examination is not carried out.

İnvazif fungal hastalığın kaba mortalitesi %40 olup; hematolojik malignitelerin mortalitesi ile benzerdir

haematologica | 2012; 97(3)

- Aspergilloza bağlı mortalite: %27-72, SSS >90

Eur J Clin Microbiol Infect Dis (2014) 33:7–21
DOI 10.1007/s10096-013-1944-3

REVIEW

Clinical and economic burden of invasive fungal diseases in Europe: focus on pre-emptive and empirical treatment of *Aspergillus* and *Candida* species

L. Drgona · A. Khachatryan · J. Stephens ·

2000-2011 arasında Avrupa'dan yayımlanan 75 çalışmanın analizi

30 günlük mortalite: %1.5 -82.4 (çoğunluğu %35-45), Aspergillus için: %30-90

Yatış ve ilaç maliyeti: 8,351-11,821 €. Tüm direkt maliyetler: 26,596-83,300 €

Table 1 Diagnostic methods in pre-emptive treatment

		Pre-emptive group criteria				
Reference	Country	Clinical	HRCT	GM/M	Microbiological	PCR
Non-comparative studies						
Maertens et al., 2005 [17]	Belgium		X	X	X	
Girmenia et al., 2010 [51]	Italy		X	X	X	
Posteraro et al., 2010 [56]	Italy			X		
Aguilar-Guisado et al., 2010 [74]	Spain	X	X		X	
Barnes et al., 2009 [79]	UK	X	X	X	X	X
Dignan et al., 2009 [82]	UK		X			
Randomised, comparative studies						
Cordonnier et al., 2009 [25]	France	X	X	X		
Hebart et al., 2009 [39]	Germany					X

GM galactomannan, *HRCT* high-resolution computed tomography, *M* mannan, *PCR* polymerase chain reaction, *UK* United Kingdom

Sık görülen invazif fungal enfeksiyonlar

Table 1 | Common invasive fungal diseases

Disease	Fungal species	Clinical outlook	Treatment options (in order of preference)	Areas for improvement
Dimorphic mycoses	• *Blastomyces dermatitidis* • *Coccidioides immitis* • *Coccidioides posadasii* • *Histoplasma capsulatum* • *Sporothrix* spp.	• Geographically restricted • Azoles > polyenes	• A vaccine would be welcomed	
Disseminated cryptococcosis	• *Cryptococcus neoformans* • *Cryptococcus gattii*	• Differences in outcome correlate with health-care resource availability • IRIS and increased ICP have been associated with the infection and need to be managed		
Invasive aspergillosis	• *Aspergillus fumigatus* • *Aspergillus flavus* • *Aspergillus terreus* • *Aspergillus calidoutus*	• Increasing resistance to azoles • Early treatment or prevention is essential	Azoles > polyenes > echinocandins	• Genetic susceptibility needs to be defined • A biomarker that can be used for diagnosis and to monitor treatment outcome would be very useful
Invasive candidiasis	• *Candida albicans* • *Candida tropicalis* • *Candida glabrata* • *Candida parapsilosis* • *Candida krusei* • *Candida auris*	• High mortality attributable to infections • Drug resistance develops in pathogens • Requires early-stage treatment	Echinocandins > azoles > polyenes	• Need better integration of new diagnostic tools with specific treatment strategies • An agent with a new mechanism of action would be advantageous for treatment
Mucormycosis	• *Rhizopus* spp. • *Mucor* spp. • *Cunninghamella bertholletiae*	• Control underlying diseases, initiate polyene therapy and consider surgery • Poor prognosis	Polyenes > azoles	• Improved diagnostics to ensure early, accurate diagnosis • Empiric therapy is not often successful

ART, antiretroviral therapy; ICP, intracranial pressure; IRIS, immune reconstitution inflammatory syndrome.

• Increasing resistance to azoles
• Early treatment or prevention is essential

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Dimorphic mycoses	• *Blastomyces dermatitidis* • *Coccidioides immitis* • *Coccidioides posadasii* • *Histoplasma capsulatum* • *Sporothrix* spp.	• Geographically restricted • Infect both immunocompetent and immunosuppressed individuals	Azoles > polyenes	• A vaccine would be welcomed and is in development • In need of more effective and oral agents, and better diagnostics for earlier identification
Disseminated cryptococcosis	• *Cryptococcus neoformans* • *Cryptococcus gattii*	• Even with ART, there are still many new cases • No new therapies in more than 25 years • Cryptococcal antigen levels are not used to monitor outcome • Differences in outcome correlate with health-care resource availability • IRIS and increased ICP have been associated with this infection and need to be managed	Amphotericin B in combination with 5-flucytosine > monotherapies	Need improved management of IRIS and ICP
Invasive aspergillosis	• *Aspergillus fumigatus* • *Aspergillus flavus* • *Aspergillus terreus* • *Aspergillus calidoutus*	• Increasing resistance to azoles • Early treatment or prevention is essential	Azoles > polyenes > echinocandins	• Genetic susceptibility needs to be defined • A biomarker that can be used for diagnosis and to monitor treatment outcome would be very useful
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- High mortality attributable to infections
- Drug resistance develops in pathogens
- Requires early-stage treatment

Erken tanı-tedavi önemli ancak gözden kaçırıyoruz?

Risk grupları net değil

Klinik bulgular (ateş?, öksürük? Cilt döküntüsü?) özgül değil

Rutin tanı testleri ayırt edici değil

Spesifik tanı testleri az sayıda, zor ve duyarlılık/özgüllük???

İNVAZİF ASPERGİLLOZ RİSKİ

YÜKSEK RİSK

- Kronik granülomatöz hastalık
- Allojenik HKHN ve GvHD
- Myelodisplastik sendrom remisyon indüksiyon tedavisi
- Akut myeloblastik lösemi remisyon indüksiyon tedavisi
- Akciğer ve/veya kalp nakli
- İnce bağırsak nakli
- Karaciğer nakli
- GvHD olmaksızın allojenik HKHN
- Akut myeloblastik lösemi konsolidasyon tedavisi

ORTA RİSK

- Akut lenfoblastik lösemi
- Kronik lenfositik lösemi
- Myelodisplastik sendrom
- Multipl myelom
- Akut alevlenme ile seyreden KOAH
- AIDS
- Non-Hodgkin lenfoma

DÜŞÜK RİSK

- Otolog HKHN
- Böbrek nakli
- Solid tümör
- Otoimmün hastalıklar (SLE vb)
- Hodgkin Lenfoma, Myeloproliferatif hastalıklar

Table 4
Risk stratification of HMs for diagnosis, phase and kind of treatment.

High risk	Intermediate risk	Low risk
AML undergoing Induction CHT with any of the following Risk Factors: Neutropenia at baseline, low CR probability (Adverse K, secondary AML), age >65 yrs., significant pulmonary disfunction, high e-TRM score.	AML not meeting criteria for High or Low Risk groups.	AML <45 yrs.; Undergoing first remission-induction or consolidation CHT and without ANY Risk Factors for IFI
AML with Prior IA		APL treated with ATRA/ATO
AML undergoing salvage regimens for Relapsed/Refractory disease.		
Allogeneic Stem Cell transplantation (from donors other than a matched sibling donor, patients active HM, GVHD requiring high-dose steroids and history of previous IFI)	Allogeneic Stem Cell transplantation (from matched sibling donors, patients in complete remission with no evidence of GVHD and no previous IFI)	
MDS/AML receiving azacitidine as salvage therapy after intensive regimens	MDS with IPSS >1.5 treated with azacitidine 75 mg/m(2) for 7 days	
	MDS during the first 2–3 cycles of AZA/Decitabine	
Acute lymphoblastic leukemia: elderly patients (≥55 y); intensive pediatric regimens (induction);HD dexametazone; previously treated (relapsed/refractory)	Acute Lymphoblastic Leukemia: Adults (30–54 y); Standard induction chemotherapy; Intensive consolidation treatment; TKI + reduced cht (Ph + ALL)	Acute Lymphoblastic Leukemia: Younger adults (30 y); Maintainance treatment (complete remission); TKI + steroids (Ph + ALL)
	Autologous Stem Cell Transplantation: Previous IFI; >3 lines of therapy (disease burden); Prolonged neutropenia (ANC <500/mm3 for more than 14 days); corticosteroid therapy; Colonization by *Candida* spp.; Previous Fludarabine treatment	MPN (Chronic Myeloid Leukemia, Essential Thrombocitemia, Idiopathic Thrombocytosis, Policytemia Vera)
	CLL treated with multiple lines of CTX Multiple myeloma in 3 or more lines or during ASCT DLBCL relapsed/refractory HD if treated with "escalating BEACOPP"	Low or high grade NHL, CLL, MM, HD treated with conventional frontline chemotherapy

AML: acute myeloid leukemia APL: acute promyelocytic leukemia MDS/AML: myelodisplastic sindromes/ acute myeloid leukemia MPN: myeloprolipherative neoplasms CLL: chronic lymphocytic leukemia MM: multiple myeloma HD: Hodgkin's disease NHL: non-Hodgkin's lymphoma.

Blood Reviews 2017;31:17–29

Hematolojik Hastalıklarda Yeni Tedavi Ajanları

AML

1. FLT3-inhibitors (Quizartinib, Midostaurin, Sorafenib)
2. Monoclonal antibodies anti-CD33 (Gentuzumab)
3. Arsenic Trioxide
4. IDH1-2 inhibitors
5. Combined liposomal cytarabine and daublastine (CTX1)

Lymphomas (low and high grade)

1. BTK-inhibitors (Ibrutinib)
2. Monoclonal antibodies anti-CD20 (Rituximab, Ofatumumab)
3. PI3Kδ signaling- inhibitor (Idelalisib)

Hodgkin's Lymphoma

1. Monoclonal antibodies anti-CD30 (Brentuximab)
2. IgG4 anti-PD-1 (Nivolumab)

ALL

1. Monoclonal antibodies
   a. anti-CD19 (Blinatuzumab)
   b. anti -CD22 (Inotuzumab)
2. TK inhibitors (Imatinib, Nilotinib, Dasatinib, Ponatinib)

Multiple Myeloma

1. IMIDS (Talidomide, Lenalidomide Pomalidomide)
2. Proteosome inhibitors (Bortezomib, Carfizomib)
3. Monoclonal antibodies
   a. anti-CD38 (Daratumumab)
   b. anti-CD319 (Elotuzumab)

CLL

1. BTK-inhibitors (Ibrutinib)
2. Monoclonal antibodies anti-CD20 (Ofatumumab)
3. PI3Kδ signaling- inhibitor (Idelalisib)
4. Anti apoptotic BCL-2 (Venetoclax)

Yeni Tedavi Ajanları ve IFI Riski

Monoklonal Antikorlar (MAbs)

B-hücre hedefleyenler:

Rituximab: NHL, HL, KLL, WM (ibrutinib ile)
Ofatumumab: KLL
Obinutuzumab: KLL, folliküler lenfoma

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
CD20	Rituximab Ofatumumab Obinutuzumab	+++	-	+	++ [2]

[2]Geç nötropeni: Rituximab sonrası sıklık %13-25, medyan süre 175 gün (77-204 gün)
Obinutuzumab'ta daha sık olma olasılığı var

Rituximab içeren tedavilerle IFI insidansında ORTA-DÜŞÜK artış söz konusu!
Artış küften çok Candida türleri ve steroid kombinasyonunda PJP 'de

Table 1. ECIL guidelines in haematology patients at risk of *Pneumocystis* pneumonia: indication

	Adults	
Indication for prophylaxis	disease/condition	duration of prophylaxis
Main (A)	ALL	from induction to end of maintenance
	allogeneic HSCT	from engraftment to ≥6 months and as long as immunosuppression is ongoing
	alemtuzumab	>6 months after completion of treatment
	fludarabine/cyclophosphamide/rituximab	≥6 months after completion of treatment
	steroids (>20 mg/day prednisone for 4 weeks)	
Optional (B)	Lymphoma treated with R-CHOP14 or escalated BEACOPP	
	nucleoside analogues (fludarabine, cladribine, mycophenolate mofetil)	
	radiotherapy for brain tumours/metastasis+high-dose steroids	

J Antimicrob Chemother 2016; 71: 2397–2404

Monoklonal Antikorlar (MAbs)

T-hücre ve B-hücre hedefleyenler:

Alemtuzumab (anti-CD52): KLL

Table 1. Novel targeted therapies: immune sequelae.

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
CD20	Rituximab Ofatumumab Obinutuzumab	+++	-	+	++ [2]
CD52	Alemtuzumab	++	+++	+	+ [3]

IFI sıklığı yüksek: IA, PJP, Mukormikoz

PJP profilaksisi önerilir

Monoklonal Antikorlar (MAbs)

T-hücre ve B-hücre hedefleyenler:

Daratumumab (anti-CD38): MM

Elotuzumab (SLAMF7): MM

Table 1. Novel targeted therapies: immune sequelae.

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
CD20	Rituximab Ofatumumab Obinutuzumab	+++	-	+	++ [2]
CD52	Alemtuzumab	++	+++	+	+ [3]
CD38	Daratumumab	+	+	-	+
SLAMF7	Elotuzumab	-	-	-	-

IFI sıklığı çok düşük

PJP profilaksisi önerilmez

Bispesifik T-Hücre Bağlayıcılar (BiTE)

Blinatumomab: B-ALL (relaps-refrakter)

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
CD20	Rituximab Ofatumumab Obinutuzumab	+++	-	+	++ [2]
CD52	Alemtuzumab	++	+++	+	+ [3]
CD38	Daratumumab	+	+	-	+
SLAMF7	Elotuzumab	-	-	-	-
CD19/CD3	Blinatumomab	+++	+	++	++

Hipogamaglobulinemi (>12 ay), nötropeni,
T hücre aktivasyonu, Sitokin fırtınası, nörotoksite (Tosilizumab/Steroid tedavisi gerektiren)

IFI sıklığında orta derecede artış!
PJP profilaksisi gerekir

Tirozin Kinaz İnhibitörleri

Bruton's Tirozin Kinaz (BTK) İnhibitörleri

BTK proteini B-hücre maturasyonu ve sağkalımı için önemli

İbrutinib: KLL, mantle-hücre lenfoma (MCL) WM, marjinal zon lenfoma (MZL)

Acalabrutinib: KLL, MCL

Zanubritinib: MCL, WM, MZL

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
CD20	Rituximab Ofatumumab Obinutuzumab	+++	-	+	++ [2]
CD52	Alemtuzumab	++	+++	+	+ [3]
CD38	Daratumumab	+	+	-	+
SLAMF7	Elotuzumab	-	-	-	-
CD19/CD3	Blinatumomab	+++	+	++	++
BTK	Ibrutinib Acalabrutinib Zanubrutinib	++	-	+	+

İA riskinde ciddi artış (öz. SSS tutulumu!) öz. ilk 6 ay

Antifungal profilaksi düşünülebilir (ileri yaş, uzamış nötropeni, refrakter hastalık, steroid)

Triazoller ile CYP3A4 üzerinden etkileşim !

Management of drug–drug interactions of targeted therapies for haematological malignancies and triazole antifungal drugs

Roger J Brüggemann, Rebecca Verheggen, Emmy Boerrigter, Marta Stanzani, Paul E Verweij, Nicole M A Blijlevens, Russell E Lewis

Lancet Haematol 2021; 9: 58–72

Over the past 10 years, the number of targeted therapies for haematological malignancies has substantially increased,

Lancet Hematol 2021;9:58-72

	Recommendations	Grade
BCL-2 inhibitors		
Venetoclax	Strong CYP3A4 inhibitors: contraindicated in the ramp-up phase, thereafter reduce the dose of venetoclax by at least 75%; if the risk of tumour lysis is low, a reduced dose of venetoclax (75% dose reduction to 25% of the standard dose) during ramp-up can be considered	D
Venetoclax	Moderate CYP3A4 inhibitors: reduce dose in the ramp-up phase by 50%, thereafter reduce the dose of venetoclax by at least 50%	D
Protein kinase inhibitors		
Idelalisib	Strong or moderate CYP3A4 inhibitors: no dose adjustment is recommended	B
Ibrutinib	Strong CYP3A4 inhibitors: reduce dose to 140 mg once a day for B-cell malignancies and to 280 mg once a day for graft-versus-host disease	D
Ibrutinib	Moderate CYP3A4 inhibitors: reduce dose to 280 mg once a day for B-cell malignancies and to 420 mg once a day for graft-versus-host disease	D
Ruxolitinib	Dual inhibitors of CYP2C9 and CYP3A4 enzymes at high dose (fluconazole >400 mg): reduce dose by 75%	D
Ruxolitinib	Strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes at low dose (fluconazole 200 mg): reduce dose by 50%	D
Ruxolitinib	Moderate CYP3A4 inhibitors: no dose alterations, monitor for toxicity	C

Azol «boosting» ekonomik olabilir! Kombine preparatlar hatayı önleyebilir!

Phosphoinositide 3-Kinase (PI3K) İnhibitörleri

PI3K proteini B-hücre sinyal yolunda görevli

Idelalisib: KLL, fL
Duvelisib:KLL, fL
Copanlisib: Relaps fL

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
PI3K	Idelalisib Copanlisib Duvelisib	++	+	-	+

Orta yüksek IFI riski, PJP profilaksisi önerilir

Janus-Associated Kinase (JAK) Inhibitörleri

JAK proteinleri reseptör dışı tirozin kinazlar. Sitokin reseptör sinyallerini kontrol ederler

Ruxolitinib: Miyelofibrozis, polistemia vera, akut /kronik GvHD

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
JAK	Ruxolitinib	-	+	-	-

İFİ riski orta-düşük
Herpes zoster riski yüksek

B-Cell Lymphoma 2 (BCL-2) İnhibitörü

BCL-2 antiapopitotik bir protein

Venetoclax: KLL, AML

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
BCL-2	Venetoclax	-	-	-	++

İFİ riski orta

PJP profilaksisi önerilir (steroid ile birlikte kullanılırsa)

Table 2. Novel targeted therapies: risk of invasive fungal infections.

Target	Agents	Risk for IFI	Prophylaxis
BTK	Ibrutinib Acalabrutinib Zanubrutinib	High	• Consider antifungal prophylaxis if other risk factors present. • PJP prophylaxis if receiving corticosteroid therapy [1].
CD52	Alemtuzumab	High	• PJP prophylaxis recommended
PI3K	Idelalisib Copanlisib Duvelisib	Moderate/High	• PJP prophylaxis recommended
CD19/CD3	Blinatumomab	Moderate	• PJP prophylaxis recommended
BCL-2	Venetoclax	Moderate	• PJP prophylaxis if receiving corticosteroid therapy [1].
CD20	Rituximab Ofatumumab Obinutuzumab	Moderate/Low	• PJP prophylaxis if receiving corticosteroid therapy [1]. • Consider for RCHOP14.
JAK	Ruxolitinib	Moderate/Low	• PJP prophylaxis if receiving corticosteroid therapy [1].
SLAMF7	Elotuzumab	Low	Minimal additional risk added
CD38	Daratumumab	Low	Minimal additional risk added
FLT3	Midostaurin Gilterinib	Low	Minimal additional risk added [2]

[1] Prednisone equivalent ≥20 mg/day for >4 weeks. [2] Given with standard induction therapy during which there is a recommendation for anti-mold prophylaxis.

Fungal Infections Potentiated by Biologics

Matthew R. Davis, PharmD[a,*], George R. Thompson III, MD[b,c], Thomas F. Patterson, MD[d]

KEYWORDS

• Monoclonal antibodies • Tyrosine kinase inhibitors • Fungal infections • Biologic • TNF-α inhibitors

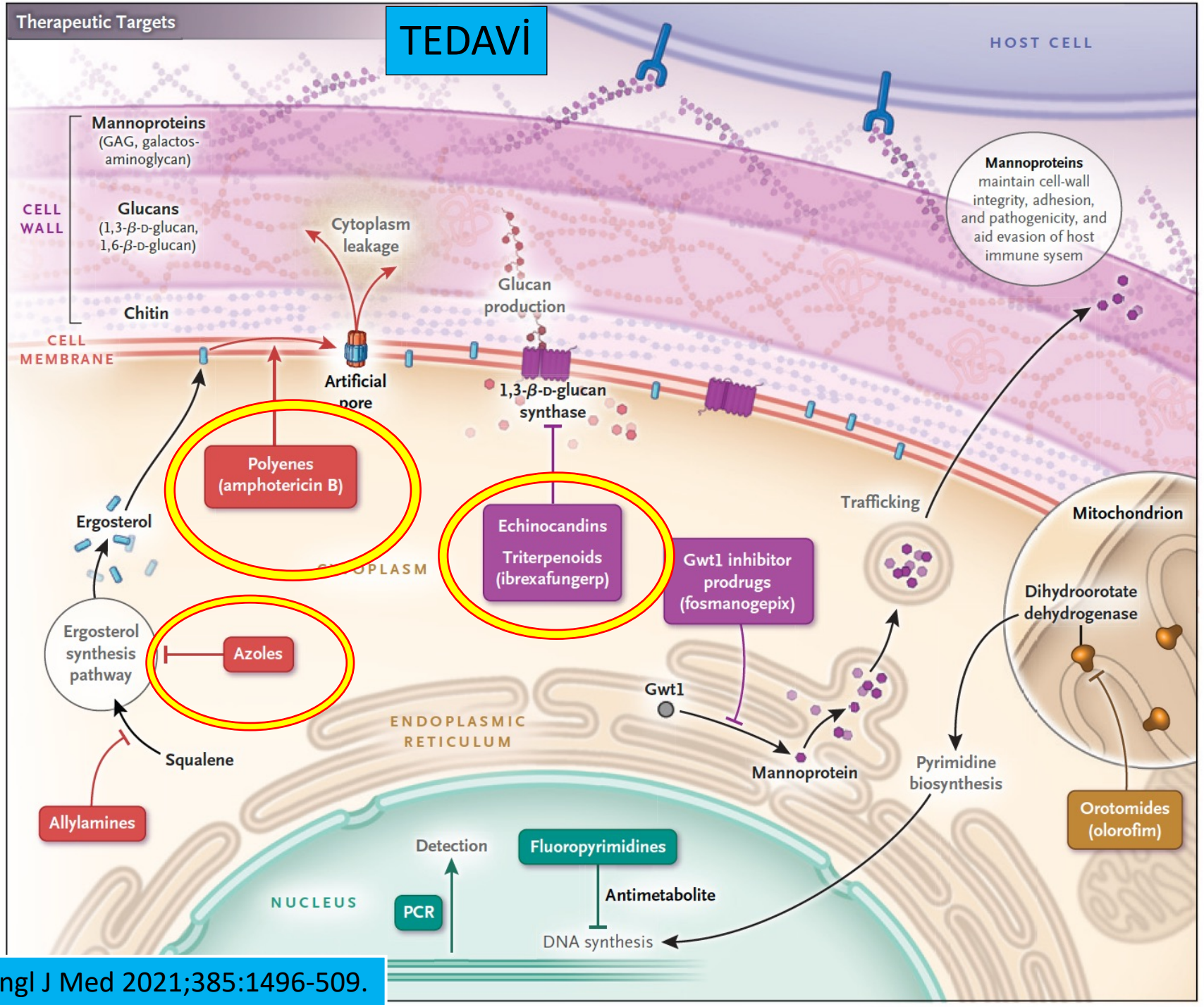
KEY POINTS

- Biologic therapies affect the immune system in intentional and unintentional ways, which can predispose patients to the development of fungal infections.
- TNF-α are used in the treatment of several autoimmune conditions and have been historically implicated in the development of opportunistic fungal infections prompting a black box warning for this commonly used biologic class.
- Ibrutinib, a Bruton kinase inhibitor, certain monoclonal interleukin inhibitors (IL), and cluster of differentiation (CD) inhibitors have also been associated with an elevated risk of fungal infections.

Infect Dis Clin N Am 2020;34:389-411

Table 2
Agents without apparent increased risk of fungal infection or insufficient data

Agent	Class	Reference
Abciximab	Glycoprotein IIb/IIIa inhibitor	125
Alefacept	T-cell costimulation modulator	148,149
Avelumab	PD-L1 inhibitor	150
Belimumab	BLyS inhibitor	151
Blinatumomab	CD19 inhibitor	110
Bosutinib	BCR-ABL inhibitor	152,153
Brentuximab vedotin	CD30 inhibitor	118
Cabozantinib	c-MET, VEGFR2, and AXL inhibitor	68
Cemiplimab	PD-1 inhibitor	154
Cetuximab	EGFR inhibitor	125
Dabrafenib	B-raf inhibitor	68
Daratumumab	CD38 inhibitor	125
Dupilumab	IL-4 inhibitor	155
Elotuzumab	SLAMF7 inhibitor	109
Epratuzumab	CD22 inhibitor	116
Gemtuzumab ozogamicin	CD33 inhibitor	125
Inotuzumab ozogamicin	CD22 inhibitor	117
Omalizumab	IgE receptor antibody	125
Palivizumab	RSV fusion protein inhibitor	125
Panitumumab	EGFR inhibitor	125
Ponatinib	BCR-ABL, PDGFR, EGFR, KIT, and FLT3 inhibitor	68
Ravulizumab	Complement C5 inhibitor	156
Trastuzumab	HER-2 inhibitor	125
Vedolizumab	Anti-integrin antibody	31



N Engl J Med 2021;385:1496-509.

Antibakteriyel İlaçlar

CLINICAL MICROBIOLOGY REVIEWS, Jan. 2011, p. 71–109 Vol. 24, No. 1
0893-8512/11/$12.00 doi:10.1128/CMR.00030-10

Challenges of Antibacterial Discovery

Lynn L. Silver*

LL Silver Consulting, LLC, 955 S. Springfield Ave., Unit C403, Springfield, New Jersey 07081

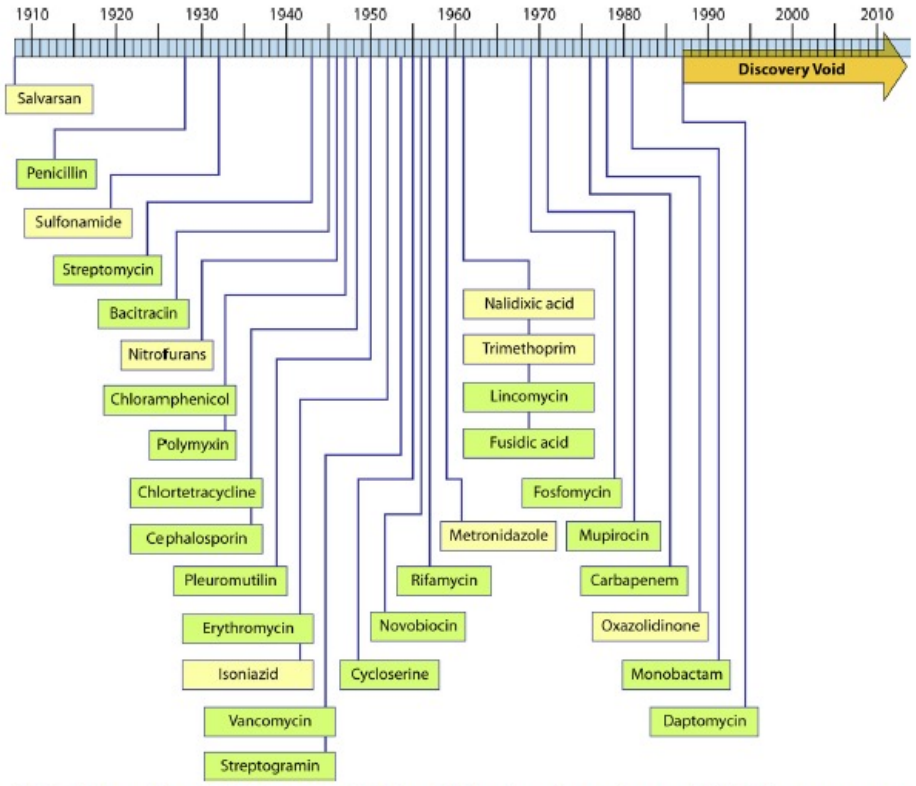
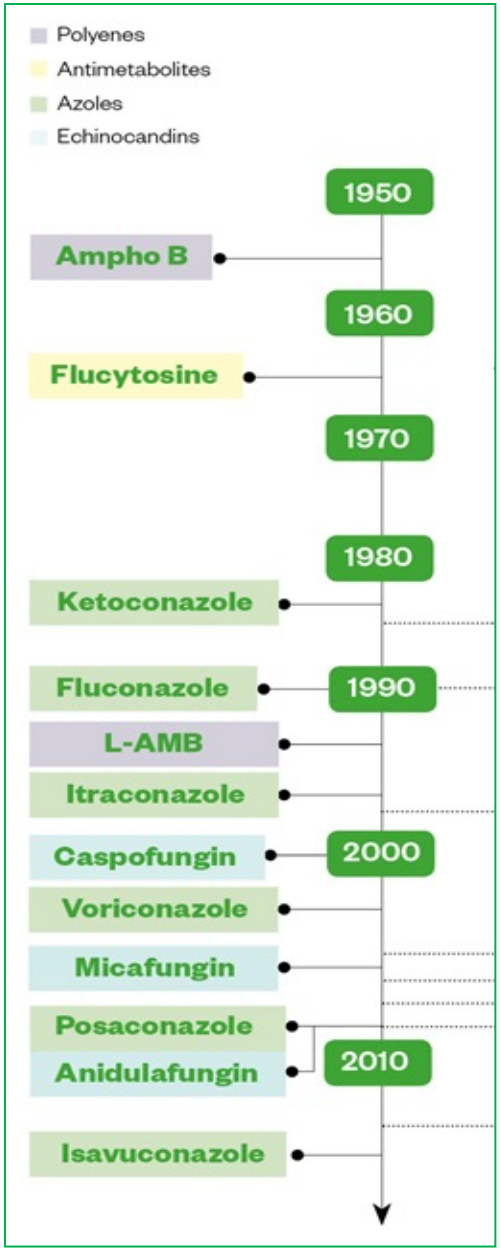


FIG. 1. Illustration of the "discovery void." Dates indicated are those of reported initial discovery or patent.

Antifungal İlaçlar



Antifungaller

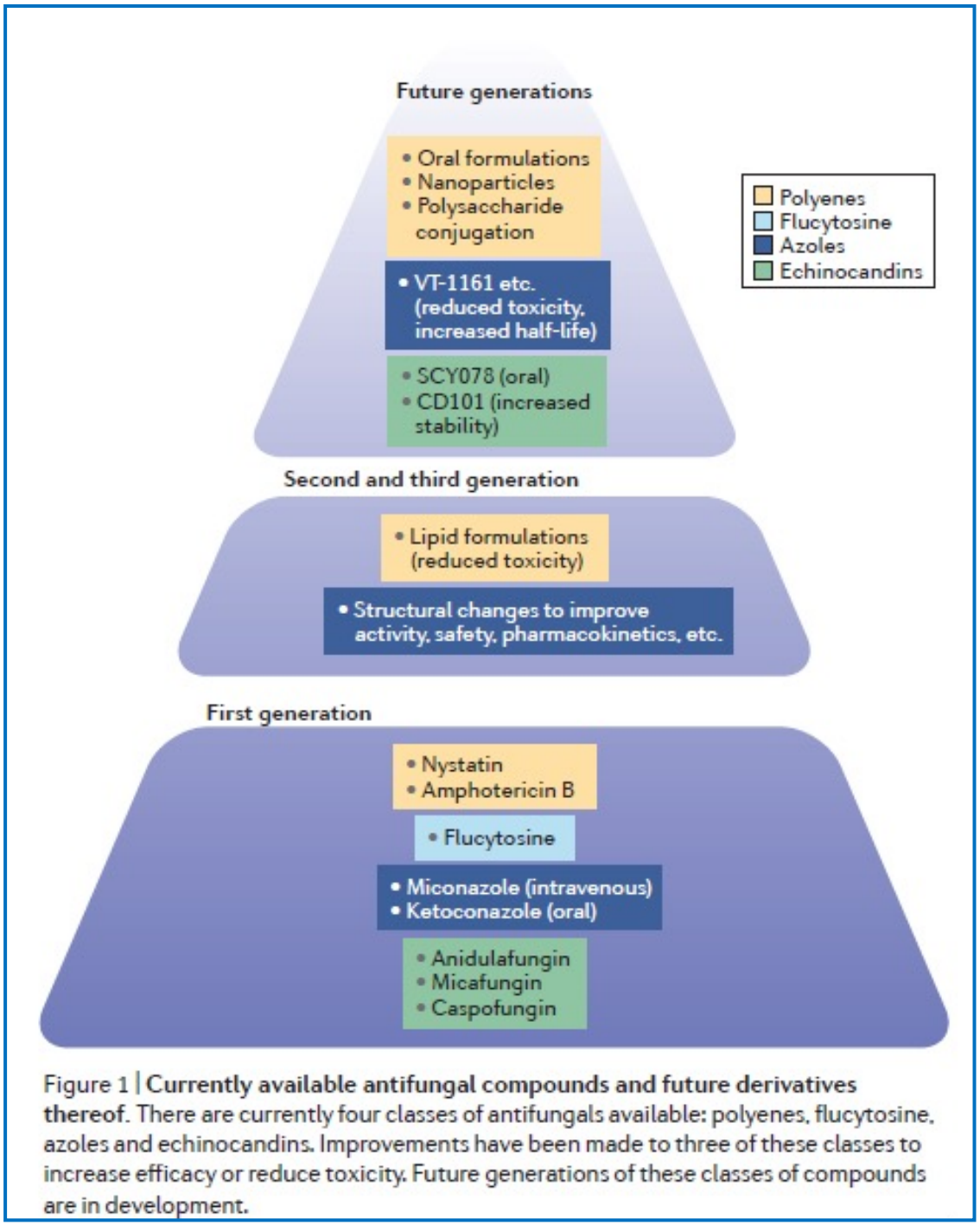
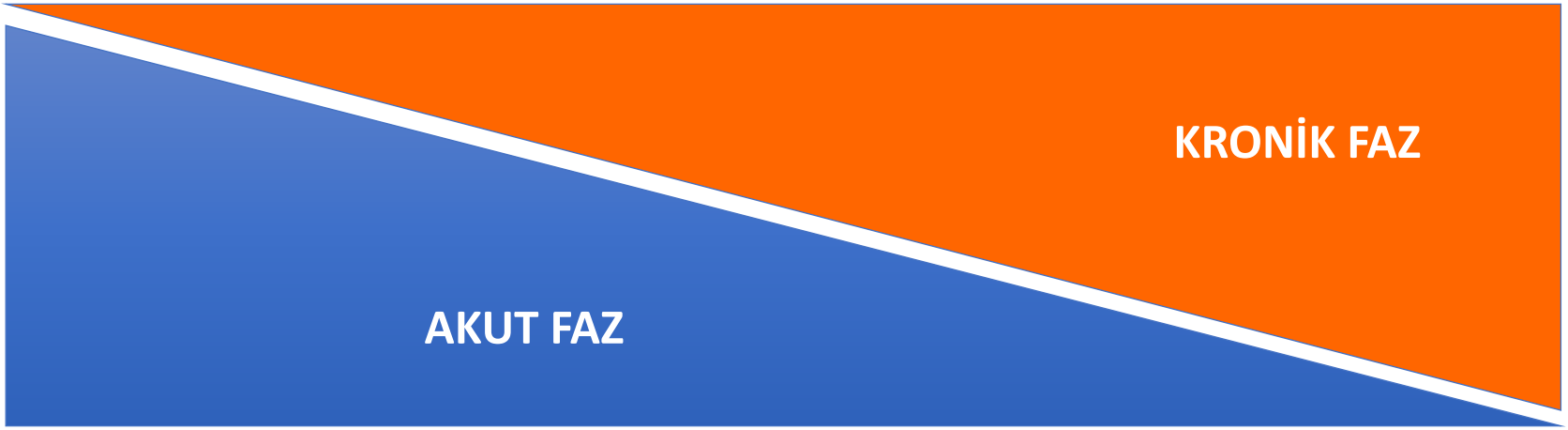


Figure 1 | **Currently available antifungal compounds and future derivatives thereof.** There are currently four classes of antifungals available: polyenes, flucytosine, azoles and echinocandins. Improvements have been made to three of these classes to increase efficacy or reduce toxicity. Future generations of these classes of compounds are in development.

FARMAKOKİNETİK ÖZELLİKLER

Spektrum	PK	Güvenlik	Rahatlık
Lipid AMB	Echinocandin	Fluconazole	Fluconazole
Posaconazole	Lipid AMB	Echinocandin	Voriconazole
Voriconazole	Fluconazole	Posaconazole	Posaconazole
Echinocandin	Voriconazole	Voriconazole	Echinocandin
Fluconazole	Posaconazole	Lipid AMB	Lipid AMB

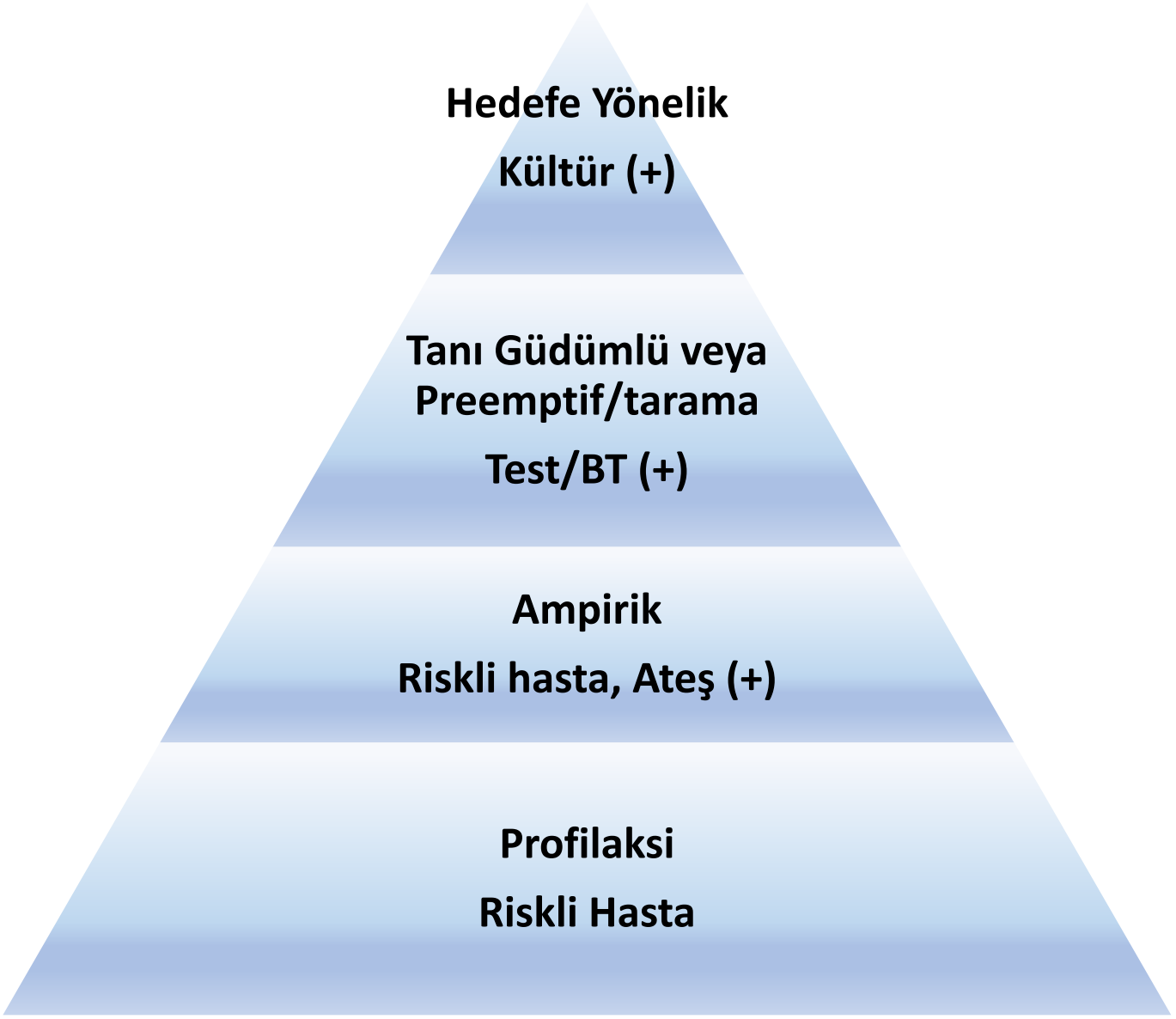


Russell E. Lewis, Importance of Pharmacokinetic Considerations for Selecting Therapy in the Treatment of Invasive Fungal Infections. Am J Therap 19, 51–63 (2012)

	Ampirik	Dissemine Kandidiyaz	Aspergilloz	Mukormikoz	Kriptokokkoz
Lipozomal AmB[1]	√	√	√	√	√
Vorikonazol[2]	-	√	√	-	-
Posakonazol[3]		-	2. basamak	-	-
Kaspofungin[4]	√	√	2. basamak	-	-
Mikafungin[5]	-	√	2. basamak	-	-
Anidulafungin[6]	-	√	-	-	-
Flukonazol[7]	-	√	-	-	√
Itrakonazol[8]	-	√	√	-	2. basamak

Referanslar: 1. AmBisome®, KÜB, Ocak 2015. 2. VFEND®, KÜB, Mayıs 2019. 3. Noxafil®, KÜB, Mart 2017. 4. Cancidas®, KÜB, Nisan 2019. 5. Mycamine®, KÜB, Nisan 2019. 6. Eraxis®, KÜB, Ocak 2019. 7. Triflucan®, KÜB, Nisan 2011. 8. İtraspor®, KÜB, Ağustos 2017.

Antifungal kullanım nedenleri (endikasyonları)



Profilaksi
Riskli Hasta

Merkezden merkeze değişse de İFİ insidansı yüksek
(AB'de 1200 hastanın prospektfi izlemi: %14, alloKHN %9, AML %18)

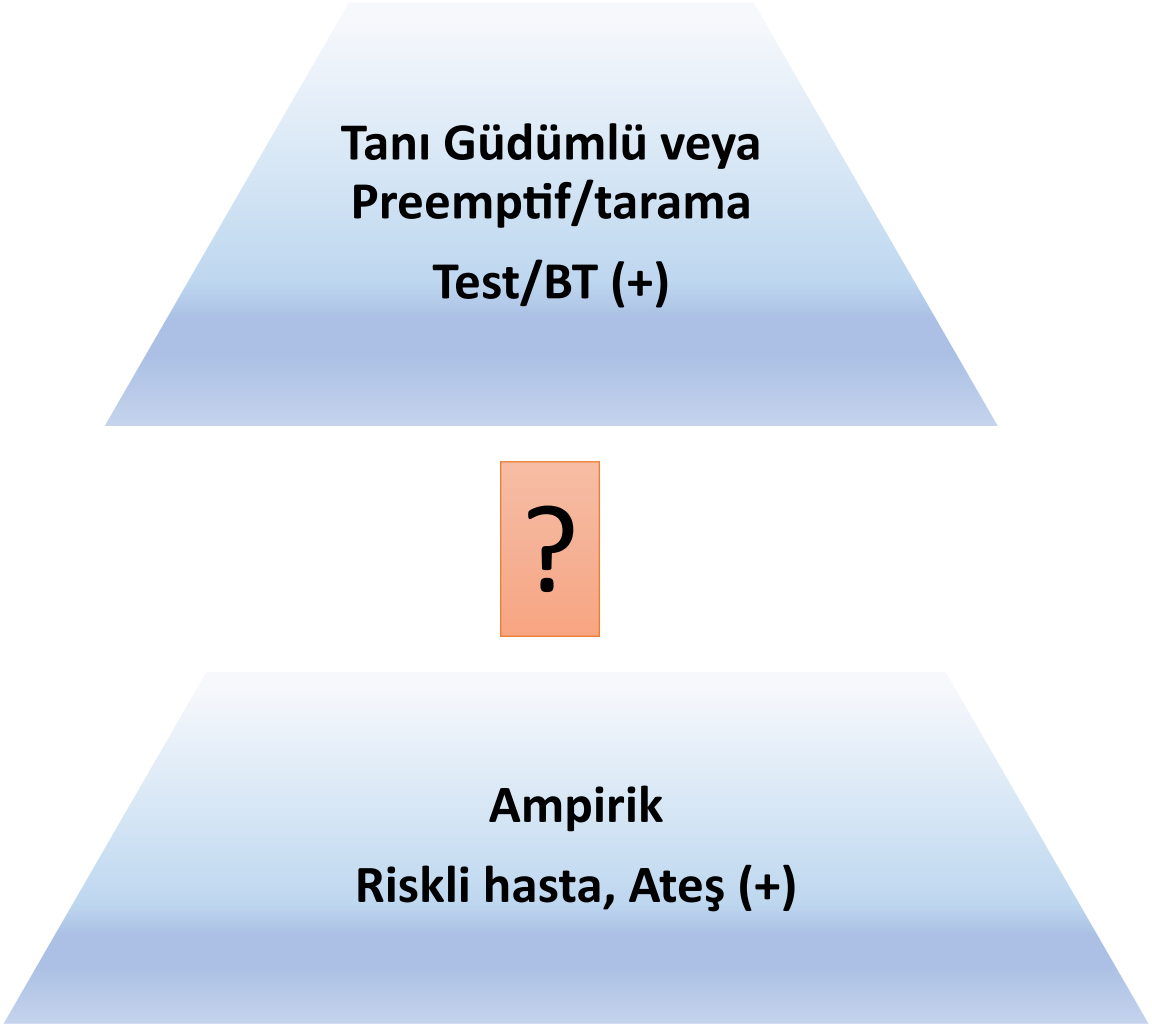
Tanı zorluğu nedeniyle gerçek insidans daha yüksek (otopsi çalışmalarında x2 - x3)

İFİ'lerin kaba mortalitesi yüksek

Risk sınıflaması yapmak, yüksek riskli hastaları belirlemek, eskisine göre daha kolay

RKÇ'lar belli gruplarda profilaksinin İFİ sıklığını azalttığını sağ kalımı artırdığını gösterdi
(AML/MDS remisyon-indüksiyon, alloKHN+GvHD)

Küflere de etkili oral uygulanabilen seçenekler var (Posakonazol)


Tanı Güdümlü veya
Preemptif/tarama
Test/BT (+)
?
Ampirik
Riskli hasta, Ateş (+)

Ampirik vs Preemptif (Tanı güdümlü) AF Tedavi

IDSA FEN rehberi:

Beklenen nötropeni süresi >7 gün, 4-7 gündür AB tdv'ne rağmen ateşi düşmeyen hastalara antifungal verilmeli (AI)

Hastanın durumu stabil, görüntüleme veya serolojik olarak mantar inf bulgusu yoksa, kültürde mantar üretilmedi ise antifungal ajan bekletilebilir (BII)

Türkiye (uzman görüşleri):

"Tanı güdümlü (preemptif) yaklaşım için farklı ünitelerde tanı araçlarına ulaşmada zorluklar söz konusu olduğundan, yüksek riskli hastalarda ampirik tedavi başlanıp, tanı testlerinden elde edilecek sonuçlara göre gerekli uyarlamaların yapılması daha doğru olur"

Turk J Hematol 2014;31:111-120

Ampirik (Düşmeyen Ateş Nedeniyle) Tedavi

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

Table 29
Fever-driven ('empiric') approach

Population	Intention	Intervention	SoR	QoE	Comment
Chemotherapy for haematological malignancies or HSCT, neutropenia <500/μL ≥96 h, fever (>38C), and parenteral broad spectrum antibacterial therapy ≥96 h (some centres consider 48 h)	Reduction in the incidence of IA and/or related mortality	Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80 kg)	A	I	Caspofungin was associated with a significantly higher rate of survival than L-AmB (subgroup analysis).
		L-AmB 3 mg/kg	B	I	Less toxicity in comparison to cAmB but more renal toxicity compared with echinocandin
		Voriconazole 6 mg/kg bid IV (oral 400 mg bid) on day 1, then 4 mg/kg bid IV (oral 200–300 mg bid)	B	II	Failed the 10% non-inferiority cut-off when compared with L-AmB, but first-line for aspergillosis. Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class. TDM
		Itraconazole 200 mg qd iv	C	II	Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class. TDM
		ABLC 5 mg/kg qd	C	I	Infusion-related toxicity (fever, chills, hypoxia)
		ABCD 4 mg/kg	C	I	Same as above
		cAmB 0.5–1 mg/kg qd	D	I	Poor tolerance due to extreme toxicity
		Micafungin 100 mg qd	B	II	
		Fluconazole	D	II_r	No activity against *Aspergillus*

Aspergilloz; ampirik tedavi (nötropeni + ateş + >96 saat AB yanıtsız)

	ECIL	ESCMID
L-AmfoB	AI	BI
Caspofungin	AI	AI
ABLC	BI	CI
ABCD	BI	CI
AmfoB-d	BI/DI*	DI
Itrakonazol	BI	CII
Vorikonazol	BI	BII
Mikafungin	BII	BII

İnvazif Aspergilloz Tedavisi

	ECIL-6	ESCMID	IDSA
Vorikonazol	AI	AI/AII	AI
L-AmfoB	BI	BII	AI
ABLC	BII	CIII	AII
Kaspofungin	CII	CII	BII
Itrakonazol	CIII	CIII	BII
Mikafungin	-	CIII	BII
ABCD	CI	DI	AII
Isavukonazol*	AI	AII	-
Vorikonazol+Anidulafungin	CI	CII	-
Kombinasyon	CIII	DIII	DII

*ülkemizde ruhsatlı değil

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

Table 23
Voriconazole therapeutic drug monitoring

Population	Intention	Intervention	SoR	QoE	Comment
All patients receiving voriconazole treatment for IA	Improve efficacy, safety and compliance	Measure plasma trough level after 2–5 days of therapy or soon after	A	II	Target range of 1–5.5 mg/L
		Repeat plasma trough level	B	II	Repeat during second week of therapy, additional samples as clinically indicated and outlined in the text
All patients receiving voriconazole prophylaxis for IA	Improve efficacy, safety and compliance of prophylaxis	Measure serum trough level after 2–5 days of therapy or soon after, and 4 days after change of dose	A	IIt	As above; most studies investigated voriconazole treatment rather than prophylaxis
Patients with IA due to *Aspergillus* strains of reduced azole susceptibility MIC 2 mg/mL	Improve efficacy of treatment for isolates with MIC 2 mg/mL	Measure serum trough level after 2 to 5 days of therapy or soon after and 4 days after change of dose	A	II	Trough >2 mg/L recommended on the basis of PK/PD analysis

Therapeutic drug monitoring (TDM) for Voriconazole is recommended if there is concern as to whether the patient is responding to treatment. TDM is only of benefit after 5 days of treatment.

Trough level < 1 mg/L: increase dose by 1mg/kg bd rounded to tablet size.

Trough level 1mg/L – 5 mg/L: continue current dose.

Trough level > 5mg/L: consider discontinuation and recommencement at lower dose.

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

Clinical Microbiology and Infection 24 (2018) e1ee38

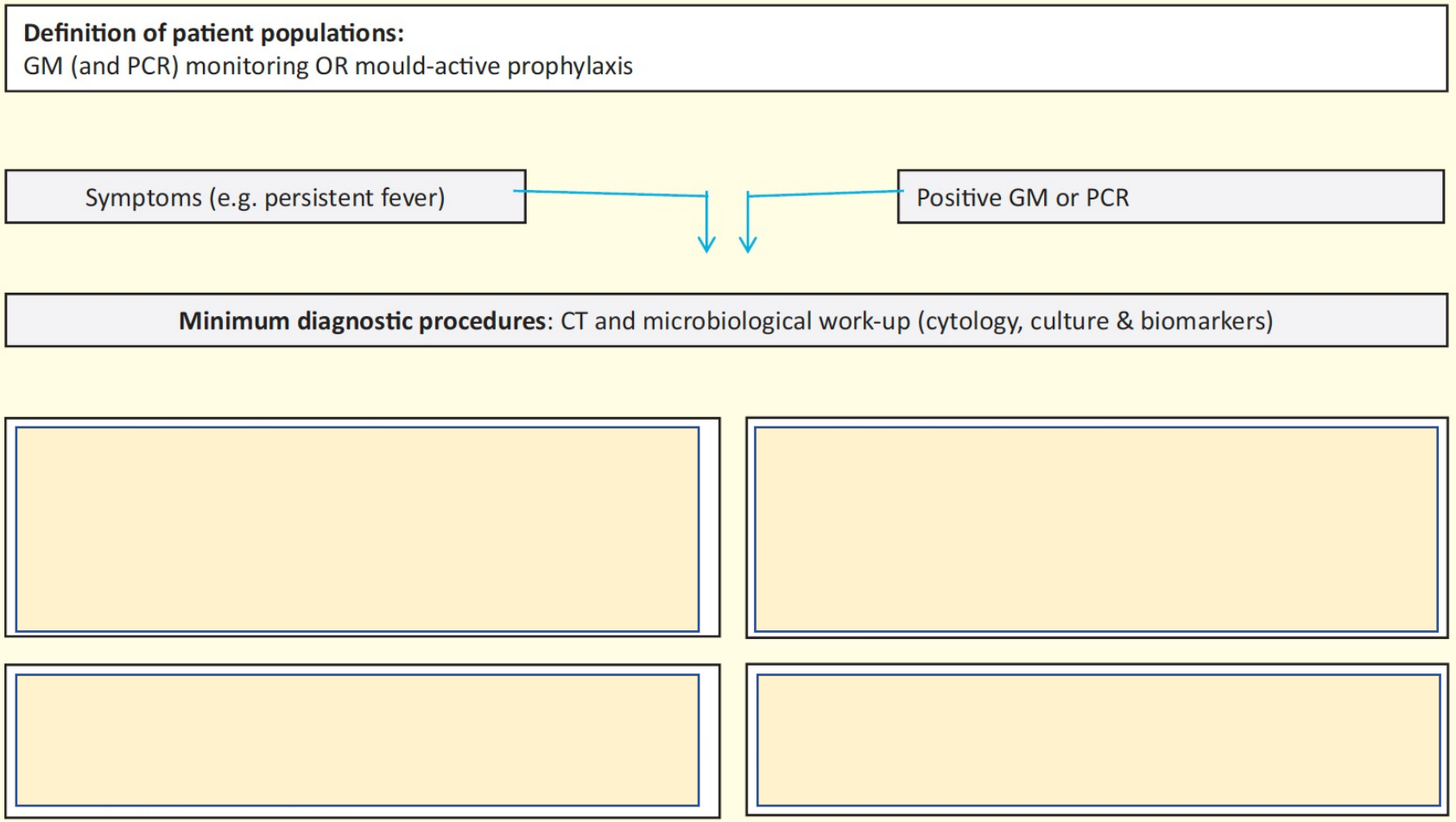


Fig. 1. Management during neutropenia.

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

Clinical Microbiology and Infection 24 (2018) e1ee38

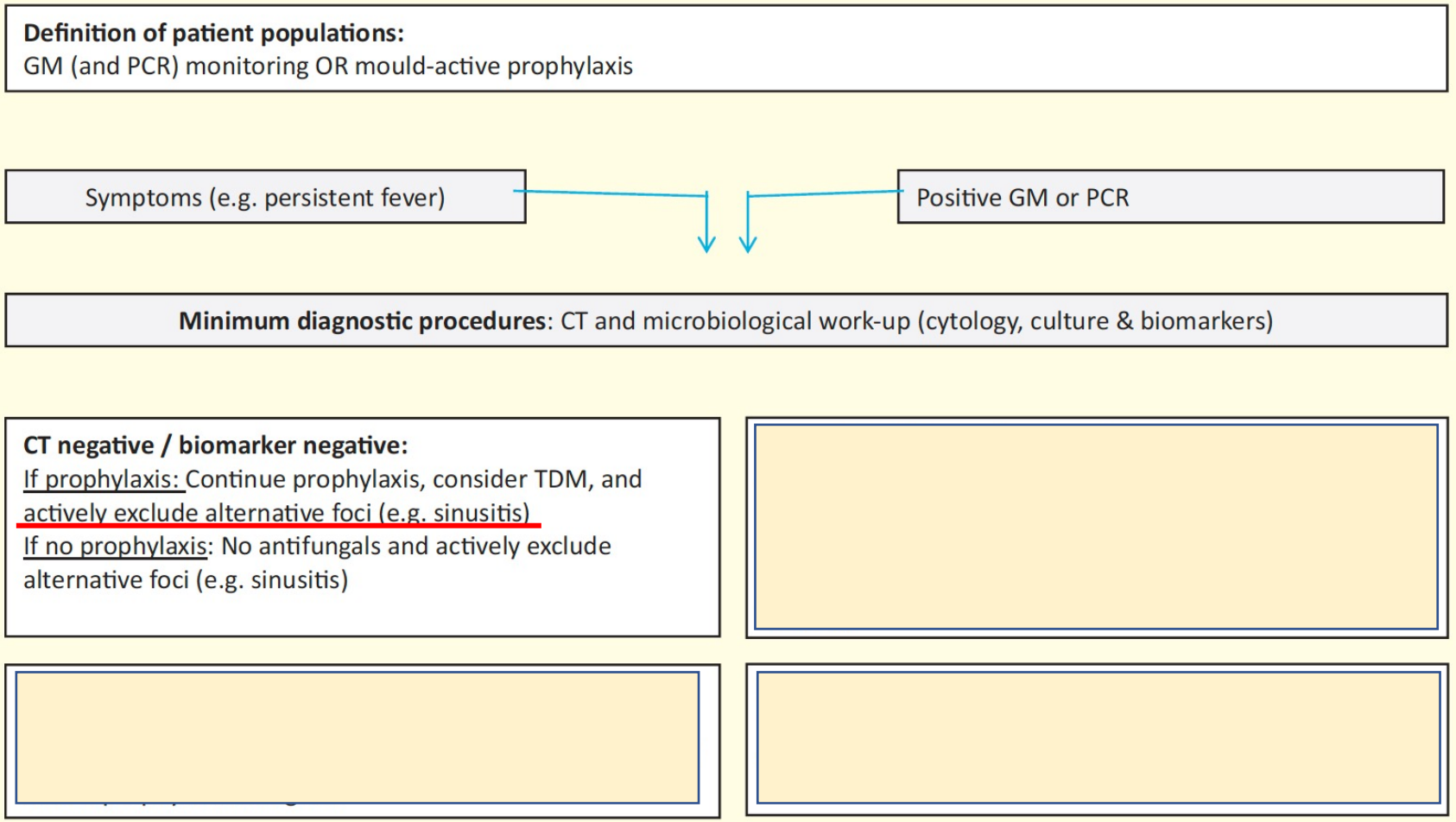


Fig. 1. Management during neutropenia.

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

Clinical Microbiology and Infection 24 (2018) e1ee38

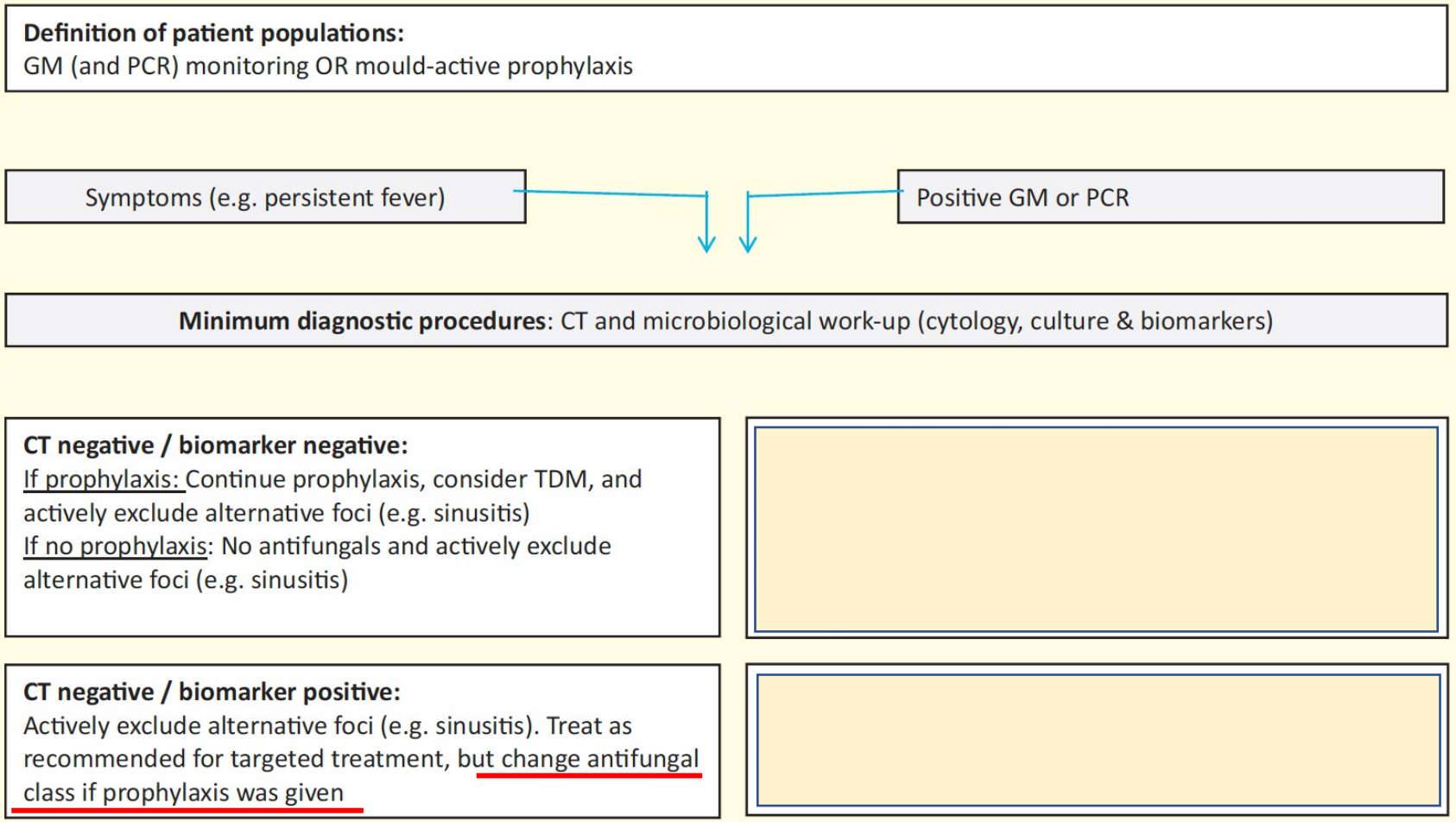


Fig. 1. Management during neutropenia.

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

Clinical Microbiology and Infection 24 (2018) e1ee38

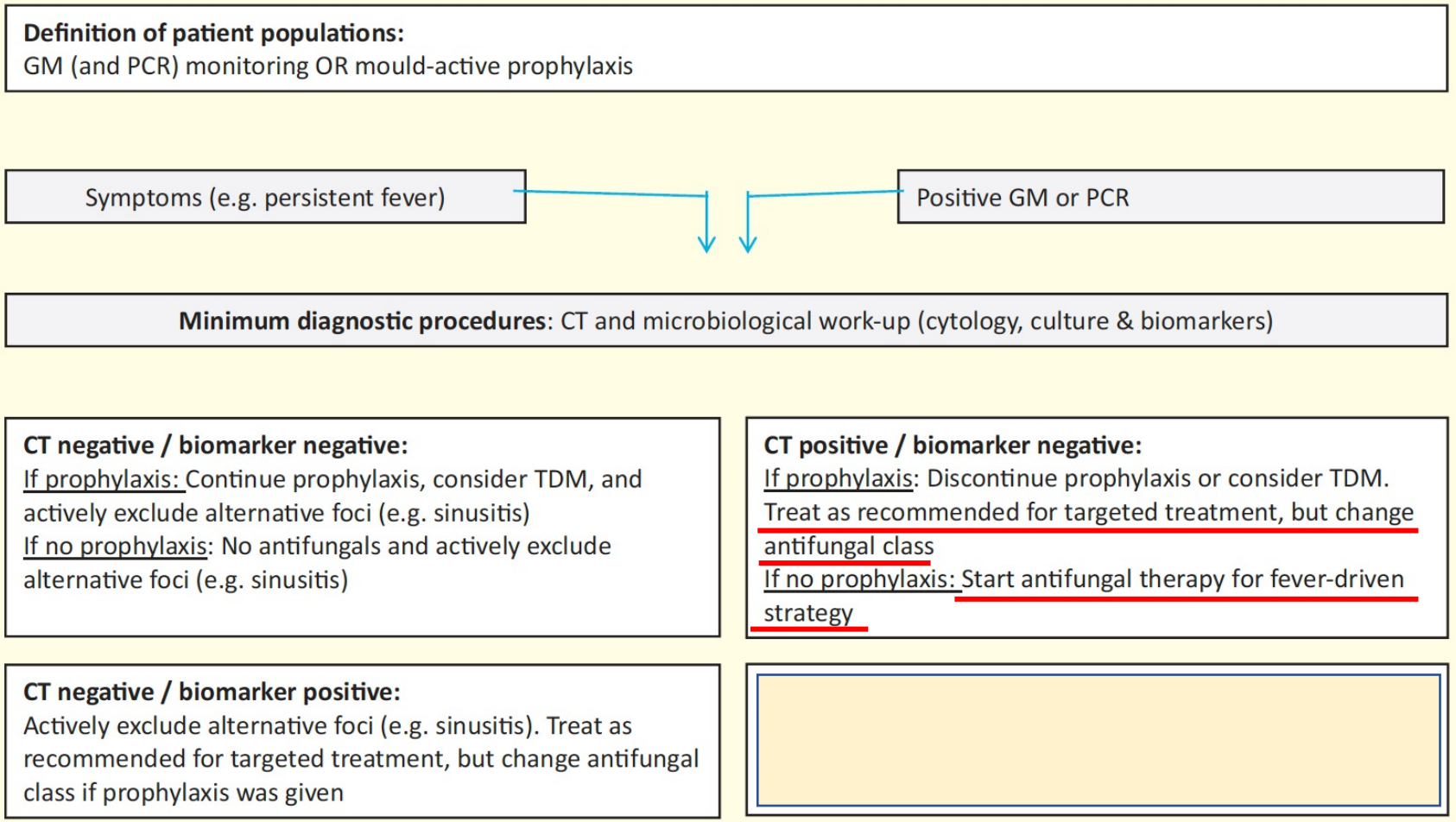


Fig. 1. Management during neutropenia.

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

Clinical Microbiology and Infection 24 (2018) e1ee38

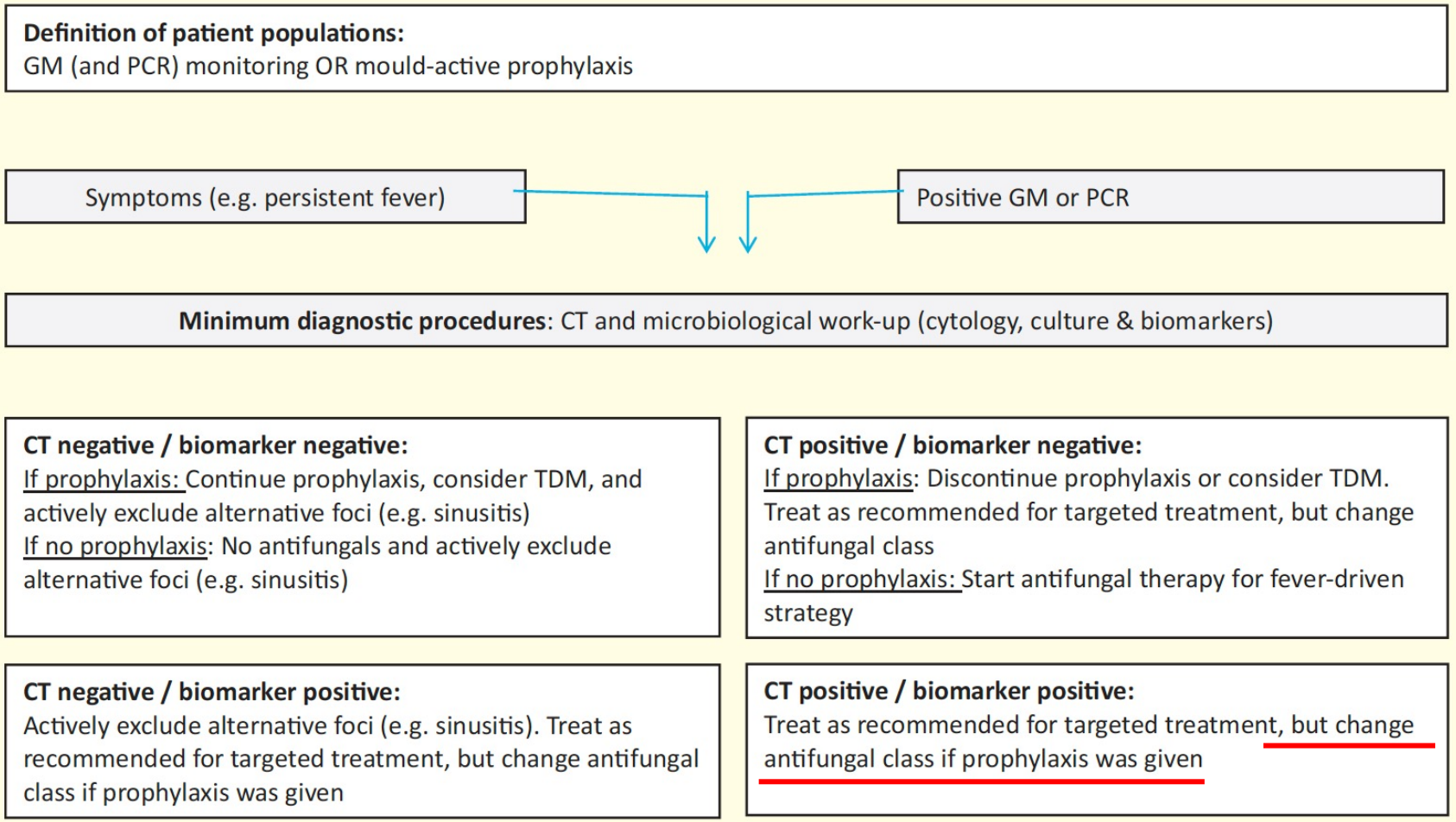


Fig. 1. Management during neutropenia.

Tedavi süresi…

Clinical Infectious Diseases Advance Access published June 29, 2016

Clinical Infectious Diseases

IDSA GUIDELINE

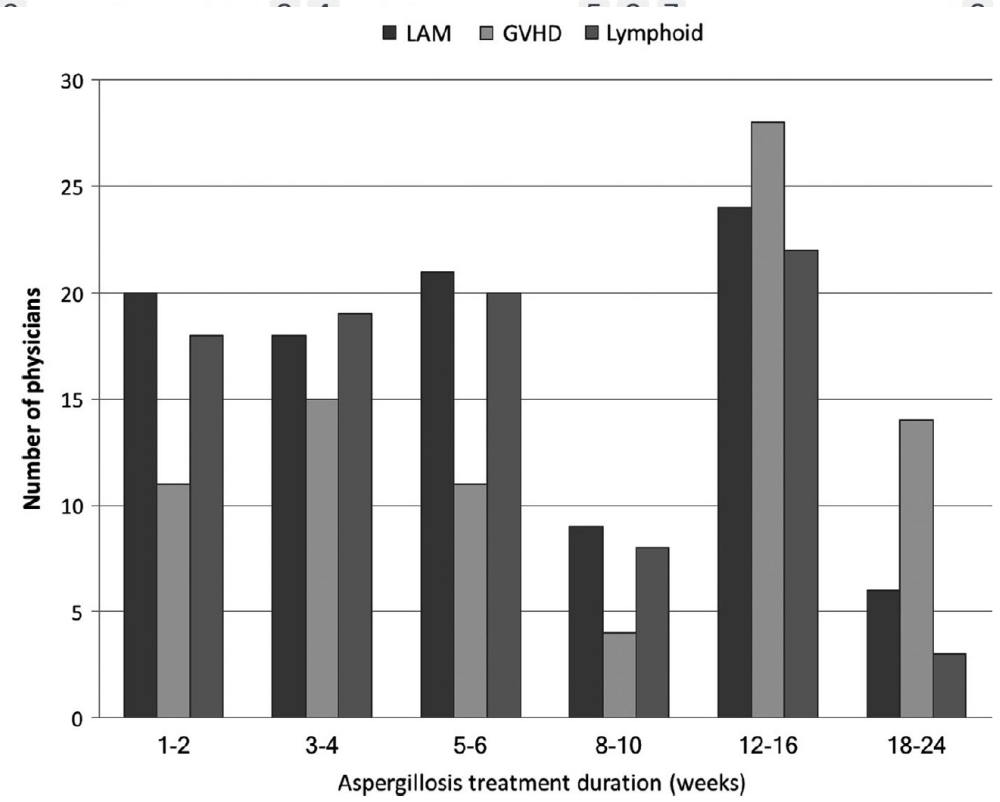
Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Duration of antifungal therapy for IPA is not well defined. We generally recommend that treatment of IPA be continued for a minimum of 6–12 weeks, depending on the severity and continuation of immunosuppression, as well as the extent of resolution of clinical disease. Therapeutic monitoring of IPA in-

Klinik ve radyolojik bulgular düzelinceye kadar, minimum 6-12 hafta

> Mycoses. 2020 May;63(5):420-429. doi: 10.1111/myc.13056. Epub 2020 Mar 4.

Invasive pulmonary aspergillosis treatment duration in haematology patients in Europe: An EFISG, IDWP–EBMT, EORTC–IDG and SEIFEM survey



Tedavi Süresi: AML 6 hafta (IQR 3-12)

ALLOKHN+GVHD: 11 hafta (IQR 4-12)

Lenfoproliferatif hastalıklar 6 hafta (IQR 3-12)

Table 4. ECIL-6 recommendations for initial first-line treatment of candidemia.

	Overall population	Hematologic patients
Antifungal therapy		
Micafungin[a]	A I	A II
Anidulafungin	A I	A II[b]
Caspofungin	A I	A II
Liposomal amphotericin B	A I	A II
Amphotericin B lipid complex	B II	B II
Amphotericin B colloidal dispersion	B II	B II
Amphotericin B deoxycholate[c]	C I	C II
Fluconazole[d,e]	A I	C III
Voriconazole[d]	A I	B II
Catheter removal[f]	A II	B II

haematologica 2017; 102(3)

Table 5. ECIL-6 recommendations for first-line treatment of candidemia after species identification.

Candida species	Overall population		Hematologic patients	
C. albicans	Echinocandins[a]	A I	Echinocandins	A II
	Fluconazole[b]	A I	Fluconazole	C III
	Liposomal amphotericin B	A I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	A II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	A II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. glabrata	Echinocandins[a]	A I	Echinocandins	A II
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. krusei	Echinocandins[a]	A II	Echinocandins[a]	A III
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
Oral stepdown	Voriconazole	B I	Voriconazole	C III
C. parapsilosis	Fluconazole	A II	Fluconazole	A III
	Echinocandins[c]	B II	Echinocandins	B III

[a]Same grading for anidulafungin, caspofungin, micafungin; [b]not in severely ill patients; [c]if echinocandin based regimen introduced before species identification and patient responding clinically and microbiologically (sterile blood cultures at 72 h), continuing use of echinocandin might be considered.

haematologica 2017; 102(3)

Table 9. ECIL-6 recommendations for first-line therapy of mucormycosis.

	Grade	Comments
Management includes antifungal therapy, surgery and control of underlying conditions	A II	Multidisciplinary approach is required
Antifungal therapy		
Amphotericin B deoxycholate	C II	
Liposomal amphotericin B	B II	Daily dose: 5 mg/kg. Liposomal amphotericin B should be preferred in CNS infection and/or renal failure
Amphotericin B lipid complex	B II	
Amphotericin B colloidal dispersion	C II	
Posaconazole	C III	No data to support its use as first-line treatment. Alternative when amphotericin B formulations are absolutely contraindicated.
Combination therapy	C III	
Control of underlying condition	A II	Includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy

haematologica 2017; 102(3)

İlaç Etkileşimleri

Sitokrom P450 enzim sistemi

- Farklı genlerin kodladığı izoenzimler:

CYP 3A4* (%30)

CYP 2D9

CYP 2D6

CYP 2D19

CYP 1A2

CYP 2E1

P-glikoprotein: efluks pompası

kapiller endotel,

hepatik kanaliküler hücreler

Böbrek tübüler hücreleri

Amfoterisin B: CYP450 ile ilgisi yok (substrat veya inhibitör değil)

Ekinokandinler: CYP450 ile ilgisi yok (substrat veya inhibitör değil)

Flukonazol: CYP 2C9, CYP 3A4 inhibitörü (doz bağımlı)

Itrakonazol: CYP 3A4, P-glikoprotein inhibitörü ve substratı

Vorikonazol: CYP 3A4, CYP 2C9, CYP 2C19 inhibitörü ve substratı

Posakonazol: CYP 3A4 inhibitörü, P-glikoprotein inhibitörü ve substratı

TABLE 2. **Cytochrome P450 (CYP) Inhibition Profile of Triazole Antifungal Agents**

Mechanism	Flu-conazole	Itra-conazole	Posa-conazole	Vori-conazole
Inhibitor				
CYP2C19	+	–	–	+++
CYP2C9	++	+	–	++
CYP3A4	++	+++	+++	++
Substrate				
CYP2C19	–	–	–	+++
CYP2C9	–	–	–	+
CYP3A4	+	+++	–	+

– = no activity; + = minimal activity; ++ = moderate activity; +++ = strong activity.

Antifungal	İlaç	Sonuç	Yorum
Triazoller	Tamoksifen	ilaç düzeyi artar	Tamoksifen toksitesi
Triazoller	Vinka alkaloidleri	İlaç düzeyi artar	Artmış nörotoksisite
Triazoller	Siklofosfamid	İlaç düzeyi artar	Hepatotoksisite
Triazoller	Docataksel, etoposid, paclitaksel, irinotecan, teniposid	İlaç düzeyi artar	Yakın takip et (klinik çalışma yok)
Vori	Imatinib	İlaç düzeyi artabilir	Ağır püstüler cilt lez., yakın takip et
Vori/posa	Siklosporin, takrolimus	İlaç düzeyi artar	İlacı yarı doza düş
Vori/posa	Sirolimus	İlaç düzeyi artar	KULLANMA
Vori/posa	takrolimus	İlaç düzeyi artar	Ilaç dozunu %66 azalt
Flu/vori	Fentanil	İlaç düzeyi artar	Yakın takip et
Vori/posa	Fenitoin	İlaç düzeyi artar	KULLANMA
Vori	Omeprazol	İlaç düzeyi artar	Ilacı %50 azalt
Vori/posa	Statinler	İlaç düzeyi artar	Statin yan etkilerine dikkat
Vori/posa	Terfenadin	QT uzar, aritmi !	KULLANMA
Vori	Rifampisin, rifabutin	Vori düzeyi düşer	KULLANMA
Vori	Sülfonilüreler	hipoglisemi	Yakın kan şekeri takibi

Caspofungin & Takrolimus

Takrolimus düzeyini %16-26, AUC'yi %20 azaltır. Düzey takibi YAP!

Caspofungin & Siklosporin

Siklosporin, Caspo düzeyini artırır: Hepatotoksisite!! KCFT takibi yap

Mikafungin & Sirolimus

Sirolimus düzeyi artar (AUC > 21%): Toksisite !!! Yakın takip et

Mikafungin & Nifedipin

Nifedipin düzeyi artar (AUC > 18%): Toksisite !!! Yakın takip et

L-AmfoB

& Antineoplastik ajanlar:

Renal toksisite, bronkospazm ve hipotansiyon artabilir.

& Kortikosteroidler / ACTH:

Hipopotasemi !! Kardiyak aritmi olabilir. K^+ takibi yap!

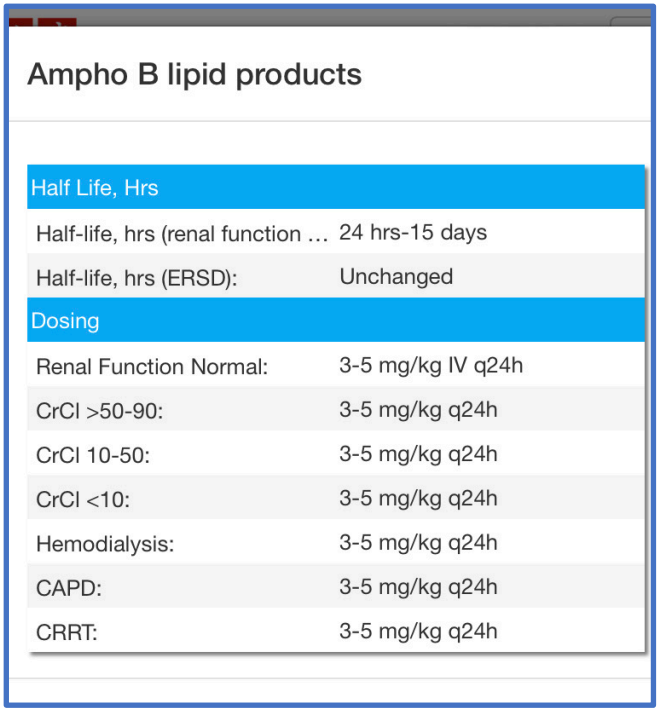
& Digoksin:

Hipopotasemi !! Digoksin düzey artışı (toksisite!!)

& Nefrotoksik ajanlar*:

Yakın BFT takibi yap!

*: Klinik çalışmalarda böbrek yetmezliği olanlarda doz ayarı yapılmadan kullanılmış



Ampho B lipid products

Half Life, Hrs	
Half-life, hrs (renal function …	24 hrs-15 days
Half-life, hrs (ERSD):	Unchanged
Dosing	
Renal Function Normal:	3-5 mg/kg IV q24h
CrCl >50-90:	3-5 mg/kg q24h
CrCl 10-50:	3-5 mg/kg q24h
CrCl <10:	3-5 mg/kg q24h
Hemodialysis:	3-5 mg/kg q24h
CAPD:	3-5 mg/kg q24h
CRRT:	3-5 mg/kg q24h

Teşekkürler…